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Association between influenza vaccination and severe outcomes in adults aged ≥ 65 years hospitalized with laboratory-confirmed influenza: a retrospective cohort study, I-MOVE hospital network, Europe, 2015/16–2024/25

Diogo F. P. Marques [a,b], Angela M. C. Rose [a], Susana Monge [c,d], Iván Martínez-Baz [e], Marijke Reynders [f], Róisín Duffy [g], Sierk D. Marbus [h], Silvia Bino[i], Petr Husa[j], Ralf Dürrwald[k], Liem Binh Luong Nguyen [l,m,n], Goranka Petrović [o], Beatrix Oroszi [p], Antonino Bella [q], Monika Kuliese [r], Stephen Abela [s], Iwona Paradowska-Stankiewicz [t], Ausenda Machado [u], Odette Popovici [v], Chris Robertson[w,x], Francisco Pozo [y,z], Ana S. Lameiras Azevedo [aa], Camino Trobajo-Sanmartín [e], Anna Parys [bb], Lisa Domegan [g], Arianne B. van Gageldonk-Lafeber [h], Lenka Součková[j], Kristin Tolksdorf [cc], Odile Launay[l,m,n], Vesna Višekruna Vučina [o], Gergő Túri [p], Flavia Riccardo [q], Ligita Jančorienė [dd], John Paul Cauchi [s,ee], Verónica Gómez [u], Mihaela Lazar [ff], Jim McMenamin[w,gg] and Baltazar Nunes [a,b]

[a]Epidemiology Department, Epiconcept, Paris, France; [b]NOVA National School of Public Health, Comprehensive Health Research Center, NOVA University Lisbon, Lisbon, Portugal; [c]National Centre of Epidemiology, Carlos III Health Institute (CNE-ISCIII), Madrid, Spain; [d]Consortium for Biomedical Research in Infectious Diseases (CIBERINFEC), Madrid, Spain; [e]Instituto de Salud Pública de Navarra – IdiSNA – CIBERESP, Pamplona, Spain; [f]Unit of Molecular Microbiology, Medical Microbiology, Department of Laboratory Medicine, Algemeen Ziekenhuis Sint-Jan, Brugge, Belgium; [g]Health Service Executive-Health Protection Surveillance Centre (HSE-HPSC), Dublin, Ireland; [h]Centre for Infectious Disease Epidemiology and Surveillance, Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; [i]Control of Infectious Diseases Department, Institute of Public Health, Tirana, Albania; [j]Faculty of Medicine, University Hospital Brno, Masaryk University, Brno, Czechia; [k]Department for Infectious Diseases, Influenza and Other Respiratory Viruses Unit, National Reference Centre for Influenza Viruses, Robert Koch Institute, Berlin, Germany; [l]Université de Paris Cité, Paris, France; [m]INSERM, I-REIVAC Network, Paris, France; [n]CIC 1417, AP-HP, Hôpital Cochin, Paris, France; [o]Division for Epidemiology of Communicable Diseases, Croatian Institute of Public Health, Zagreb, Croatia; [p]National Laboratory for Health Security, Epidemiology and Surveillance Centre, Semmelweis University, Budapest, Hungary; [q]Department of Infectious Disease, Istituto Superiore di Sanità, Rome, Italy; [r]Department of Infectious Diseases, Lithuanian University of Health Sciences, Kaunas, Lithuania; [s]Infectious Disease Prevention and Control Unit (IDCU), Health Promotion and Disease Prevention, Msida, Malta; [t]National Institute of Public Health National Institute of Hygiene – National Research Institute, Warsaw, Poland; [u]Department of Epidemiology, National Institute of Health Doctor Ricardo Jorge, Lisbon, Portugal; [v]National Centre for Surveillance and Control of Communicable Diseases, National Institute of Public Health Bucharest, Romania; [w]Clinical and Protecting Health Directorate, Public Health Scotland, Glasgow, UK; [x]University of Strathclyde, Glasgow, UK; [y]National Centre for Microbiology (CNM-ISCIII), Institute of Health Carlos III, Madrid, Spain; [z]Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Spain; [aa]Directorate-General of Public Health, Valencia, Spain; [bb]National Influenza Centre, Sciensano, Brussels, Belgium; [cc]Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany; [dd]Clinic of Infectious Diseases and Dermatovenerology, Institute of Clinical Medicine, Medical Faculty, Vilnius University, Vilnius, Lithuania; [ee]Queen Mary University of London, Malta Campus, Gozo; [ff]National Institute of Research and Development for Microbiology and Immunology"Cantacuzino", Bucharest, Romania; [gg]University of Glasgow, Glasgow, UK

ABSTRACT

Introduction: Older adults face an increased risk of influenza-related intensive care unit (ICU) admission and in-hospital death (IHD). Although vaccination reduces hospitalization, its effect on these outcomes remains uncertain. We estimated the association between influenza vaccination and both outcomes among adults aged ≥65 years hospitalized with laboratory-confirmed influenza.

Research design and methods: We conducted a retrospective cohort study using European I-MOVE hospital network data (2015/16–2024/25); vaccination was defined as vaccine receipt ≥14 days before symptom onset. We estimated pooled-season adjusted risk ratios (aRR) using Poisson regression adjusting for potential confounders. We calculated relative risk reduction (RRR) as (1−aRR)×100, overall and by age group (65–79, ≥80 years).

Results: After exclusions, 4,257 patients (five study sites, six seasons) were included. ICU admission occurred in 3% of vaccinated and 5% of unvaccinated patients; IHD occurred in 5% of both groups. RRR was 11% (95% CI: −21–34) against ICU admission (65–79 years: −4%; ≥80 years: 44%). RRR against IHD was 26% (95% CI: 3–43); 17% and 29% in each respective age group.

Conclusions: Vaccination showed little or no association with ICU admission, but was associated with a one-quarter reduction in IHD among hospitalized older adults, reinforcing its benefits against fatal in-hospital outcomes.

PLAIN LANGUAGE SUMMARY

Older adults hospitalized with influenza may experience severe outcomes, such as admission to an intensive care unit (ICU) or death during their hospital stay. While influenza vaccines are known to

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CONTACT Diogo F. P. Marques d.marques@epiconcept.fr Epidemiology Department, Epiconcept, Paris, France

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reduce the risk of hospitalization, it is less clear whether they also reduce the risk of these severe outcomes once someone is already hospitalized. We analyzed data from a large European hospital network that collected information over several influenza seasons between 2015 and 2025. The study included 4,257 adults aged 65 years and older who were admitted to hospital and tested positive for influenza virus. We compared the risk of severe outcomes between vaccinated and unvaccinated people. Among vaccinated people positive for influenza virus, about 3 in 100 were admitted to an ICU, compared with about 5 in 100 unvaccinated people. Death in hospital occurred in about 5 in 100 people in both groups. After taking age, sex, long-term health conditions, timing of admission, season and study site into account, vaccination showed little or no clear association with ICU admission. In contrast, vaccinated individuals had a lower risk of dying in hospital than unvaccinated individuals. This corresponded to about a one-quarter reduction in the risk of death. This finding suggests that influenza vaccination may provide additional benefits in reducing the risk of death among older adults who are hospitalized with influenza, even when hospital admission is not prevented, supporting continued efforts to improve vaccine uptake in this high-risk population.

1. Introduction

Seasonal influenza remains a major cause of morbidity and mortality worldwide, particularly among older adults [1]. Individuals aged 65 years account for a substantial proportion of influenza-associated hospitalizations and deaths [2]. Immunosenescence combined with a higher prevalence of underlying chronic conditions, contributes to the elevated risk of in-hospital severe outcomes such as intensive care unit (ICU) admission and in-hospital death (IHD) [3,4].

Influenza vaccination is recommended in Europe for older adults and other high-risk groups to reduce the burden of severe disease [5]. However, vaccine coverage varies across seasons and countries in the European region. According to Eurostat data spanning 2015–2023, the median seasonal influenza vaccination coverage among individuals aged 65 years and over was 42%, from 40% in 2015 to 47% in 2023 [6]. Although influenza vaccination is effective at preventing visits to primary health care and reducing hospital admissions for laboratory-confirmed influenza [7], infections among vaccinated individuals still occur [8]. In such cases, vaccination may still reduce the risk of severe in-hospital outcomes; however, existing evidence largely comes from single-country studies or is restricted to a limited number of influenza seasons, which precludes evaluating whether this association is consistent over time [8]. Understanding whether influenza vaccination is associated with a lower risk of in-hospital severe outcomes among hospitalized patients with influenza diagnosis, particularly in more vulnerable individuals, is relevant for public health communication and vaccination policy.

Since 2015/16, the I-MOVE (Influenza–Monitoring Vaccine Effectiveness in Europe) hospital network has conducted multicenter studies using harmonized protocols to estimate influenza vaccine effectiveness (VE) against laboratory-confirmed influenza hospitalization among patients with severe acute respiratory infection (SARI) [9]. In 2021, this network became part of the VEBIS (Vaccine Effectiveness, Burden and Impact Studies) project, maintaining the use of a common protocol [10]. The availability of harmonized and multi-season data from several European countries within the I-MOVE network provides a unique opportunity to pool data across influenza seasons and study sites, increasing sample size and thus precision of estimates. In this study, we aimed to estimate the association between seasonal influenza vaccination and in-hospital severe outcomes among adults aged ≥65 years hospitalized with laboratory-confirmed influenza across the 2015/16–2024/25 seasons, using data from the European I-MOVE hospital network.

2. Methods

2.1. Study design, data collection and study period

We conducted a retrospective cohort study nested within a test-negative design study. We pooled multi-country hospital data (17 study sites in 16 countries) from the European I-MOVE network, covering the 2015/16–2024/25 influenza seasons. We obtained permission from study site representatives to use these data. All study sites followed a common generic protocol for patient recruitment and data collection [11,12]. Patient recruitment was either exhaustive or systematic during periods of high workload (e.g. inclusion on pre-specified days). Demographic, clinical, and vaccination information were collected using standardized methods through interviews and/or consultation of electronic medical records. Informed consent was obtained in accordance with local ethical requirements. Within each influenza season, the study period began either 14 days after the start of the national influenza vaccination campaign or from the symptom onset week of the first laboratory-confirmed influenza case, whichever occurred later. In each season, the study period ended at the last week of symptom onset for a confirmed case or week 20, whichever occurred earlier.

We defined a study site as a country or region with at least one participating hospital.

2.2. Study population, follow-up, outcome and exposure definitions

The study population consisted of community-dwelling hospitalized patients aged ≥65 years who met the SARI case definition and tested positive for influenza virus by RT-PCR during their admission and ≤7 days after onset of symptoms. The SARI case definition varied slightly between the pre- and post-COVID-19 pandemic periods of the I-MOVE hospital network, reflecting protocol updates implemented with the expansion of the network to estimate COVID-19 VE. During the pre-pandemic period (2015/16–2019/20), SARI was defined as

any patient hospitalized for ≥24 hours with at least one systemic symptom (fever or feverishness, malaise, headache, myalgia or deterioration of general condition) and at least one respiratory symptom (e.g. cough, sore throat or shortness of breath) at admission or within 48 hours after admission. During the pandemic and post-pandemic period (2020/21–2024/25), SARI was defined as any patient hospitalized for ≥24 hours with either: fever, cough, or shortness of breath at admission or within 48 h after admission [11,12].

Within each season, influenza virus-positive patients entered the cohort at hospital admission (time zero) and were followed until hospital discharge. The outcomes of interest were ICU admission and IHD, both handled as categorical variables (Yes/No/Missing). ICU admission was defined as admission to an intensive care unit at any point during the hospital stay, based on clinical records or hospital coding. IHD was defined as death occurring during hospitalization, determined from vital status at discharge. To prevent outcome misclassification, we restricted the analysis to patients with a complete hospital course. Consequently, patients whose data were extracted prior to discharge, or who lacked a discharge status (alive or dead), were excluded from the analysis, as ICU admission or death could still occur later during hospitalization. Although the specific causes of ICU admission or IHD were not available, these outcomes occurred during the hospitalization with laboratory-confirmed influenza virus.

The exposure of interest was influenza vaccination. We classified patients as vaccinated if they received any influenza vaccine ≥14 days before symptom onset in the same season. Those vaccinated 1–13 days before onset were excluded, and those not vaccinated or vaccinated on or after onset were considered unvaccinated.

2.3. Data pooling and exclusions

We used season-specific datasets for 'all laboratory-confirmed influenza' as well as separate datasets for influenza A(H1N1) pdm09, A(H3N2) and B viruses. These data had already undergone standardized data cleaning and exclusion procedures (e.g. removal of healthcare workers, residents of long-term care facilities, records with inconsistent dates) as described in previous I-MOVE publications [7,9,13–18]. We then pooled the season-specific records into a multi-season dataset for each influenza virus (sub)type.

For each of these pooled datasets, we applied a stepwise exclusion procedure to the ICU and IHD outcomes independently. This approach was used to minimize potential reporting bias and avoid sparse data. First, within each study site and season, we excluded hospitals with more than 10% of patients missing outcome information. We subsequently excluded study sites contributing fewer than five outcome events, removed influenza seasons represented by only one contributing study site and excluded individual records with missing outcome data.

To ensure comparability between outcomes and that both analyses were conducted on the same underlying population, we restricted the data to patients with complete data for both outcomes (aligned cohort). Finally, we excluded patients with documented co-infection with SARS-CoV-2 and/or respiratory syncytial virus (RSV), to ensure the analysis population reflected severe outcomes attributable to influenza virus. We only performed the analysis for a given influenza virus (sub) type if, after exclusions, there were at least 3 seasons to ensure that pooled season estimates had a better coverage of the period under study.

2.4. Statistical methods

We estimated the association between influenza vaccination and the risk of ICU admission or IHD using both one- and two-stage pooling approaches. Using a single aligned dataset, we fitted separate modified Poisson regression models for each outcome. These models utilized a log link and robust standard errors to estimate confounder-adjusted risk ratios (aRRs) comparing vaccinated with unvaccinated influenza virus-positive patients. We quantified relative risk reduction (RRR) as (1-aRR) x 100 (expressed as a percentage), which was used to describe the magnitude of the association between vaccination status and each outcome.

For the one-stage pooling approach, we adjusted models for age, sex, presence of at least one commonly collected chronic condition (diabetes, chronic lung disease/asthma, cardiovascular disease, or immunodeficiency), admission date, season and study site. We explored three functional forms for age: a linear term, restricted cubic splines (RCS) with 3–4 knots and a categorical variable (65–79, ≥80 years). We evaluated several parameterizations for admission date to account for seasonal and within-season variation: (i) categorical variables combining season with admission month or week; (ii) additive fixed effects for season and admission month or week; and (iii) the admission date modeled as a continuous daily index (representing the chronological sequence of days since the study start) via RCS with 3–4 knots, included as both an additive term and an interaction with season. The final specification was selected based on the Akaike Information Criterion (AIC). We estimated RRR overall (≥65 years) and stratified by age group (65–79, ≥80 years). Additionally, we conducted a secondary analysis stratified by pre- and post-pandemic period to assess the potential impact of changes in healthcare systems and respiratory virus circulation. We assessed effect modification by age group and pre/post-pandemic period by including interaction terms between vaccination status and the respective variable in the adjusted models.

For the two-stage analysis, we first fitted season-specific adjusted models using the same modified Poisson framework and AIC-selected specifications for age and admission date. We then pooled the log risk ratios across seasons using a fixed-effects meta-analysis and quantified between-season heterogeneity using the I^2 statistic.

We flagged results as potentially unstable when the number of outcomes divided by 10 was smaller than the number of model parameters or contributing study sites. When this occurred, we also fitted a Firth-type penalized modified Poisson regression [19] to identify the presence of small-sample bias. We compared the RRR from standard and penalized models and did not report estimates where the absolute difference exceeded 10% points.

2.5. Sensitivity analyses

We conducted four sensitivity analyses. To evaluate the impact of our exclusion criteria, we estimated the RRR by (1) including hospitals with >10% missing outcome data; (2) utilizing outcome-specific complete-case populations rather than the aligned cohort; and (3) including patients with SARS-CoV-2 or RSV co-infections. Finally, to evaluate the robustness of our findings against unmeasured confounders, (4) we performed a quantitative bias assessment (QBA) by calculating E-values [20] for estimates whose 95% confidence interval excluded the null.

All data analyses were performed using R statistical software (v4.5.2, R Core Team).

3. Results

3.1. Descriptive analysis

Of the four pooled-season datasets created (all laboratory-confirmed influenza, A (H1N1)pdm09, A(H3N2), and influenza B), only the dataset for all laboratory-confirmed influenza met the inclusion criteria for analysis (at least three seasons remaining after exclusions; see Supplementary Figures S1–S3 for the flowcharts of exclusions for the other (sub)types). This dataset contained 8,640 influenza virus-positive hospitalized patients aged ≥65 years from 17 study sites participating in the I-MOVE hospital network between the 2015/16 and 2024/25 influenza seasons. After applying exclusion criteria, 4,257 patients from five study sites and 63 hospitals were included across six seasons, three in the pre- (2016/17–2018/19) and three in the post-pandemic period (2022/23–2024/25) (Figure 1).

Among the patients included in the final analysis, 59% (n = 2,490) were vaccinated against influenza. Vaccinated patients were older than unvaccinated patients (59% vs 43% were aged ≥80 years) and slightly more likely to have at least one chronic condition (87% vs 81%). The sex distribution was similar between groups, with a slightly higher proportion of males among vaccinated patients (52%) compared with unvaccinated patients (48%). Among those vaccinated, standard-dose vaccines were the most common vaccine type (72%), followed by adjuvanted (17%) and high-dose (9%) vaccines. The administered vaccines were approximately even split between trivalent and quadrivalent formulations. Patients were enrolled across six influenza seasons, with the largest contribution from the 2024/25 season; the seasonal distribution was broadly similar between vaccinated and unvaccinated groups (Table 1). The distribution of vaccinated and unvaccinated patients by participating study site and season is detailed in Supplementary Table S1.

The distribution of influenza virus (sub)types varied by season, with three seasons showing influenza A (H3N2) predominance (2016/17, 2018/19 and 2022/23), one with influenza B predominance (2017/18) and two with higher prevalence of influenza A(H1N1)pdm09 (2023/24 and 2024/25) (Figure 2).

Patient characteristics remained broadly similar across the pre- and post-pandemic periods, except for vaccine type and circulating subtypes. Standard-dose (egg-based, non-adjuvanted inactivated) vaccines predominated in the pre-pandemic period (94%), whereas the post-pandemic period saw a higher use of adjuvanted (29%) and high-dose (18%) vaccines. Furthermore, while influenza A(H3N2) was the most frequent subtype in the pre-pandemic period (62%), the post-pandemic period was marked by a higher proportion of A (H1N1)pdm09 (41%), than A(H3N2) (31%) (Supplementary Table S2).

Among all included patients aged ≥65 years, ICU admission occurred in 3% of vaccinated and 5% of unvaccinated patients, while IHD occurred in 5% of patients in both groups. Among patients aged 65–79 years, ICU admission occurred in 6% of vaccinated and 7% of unvaccinated patients, and IHD occurred in 3% of both vaccinated and unvaccinated groups. Among patients aged ≥ 80 years, ICU admission occurred in 1% of vaccinated and 3% of unvaccinated patients, and IHD occurred in 6% and 9%, respectively (Table 2).

When stratifying by pre- and post-pandemic period, the risk of ICU admission was 3% among vaccinated and 4% among unvaccinated patients in the pre-pandemic, compared to 4% and 6% in the post-pandemic period, respectively. For IHD, the risk was 4% among vaccinated and 3% among unvaccinated patients in the pre-pandemic, and 5% and 7% in the post-pandemic period (Supplementary Table S3).

3.2. Relative risk reduction in ICU admission and in-hospital death

The pooled-season RRR for ICU admission was 11% (95% CI: −21–34), with age-specific estimates of −4% (95% CI: −46–25) among patients aged 65–79 years and 44% (95% CI: −11–72) among those aged ≥ 80 years (Table 2). The ratio of aRRs comparing patients aged ≥80 years with those aged 65–79 years was 0.46 (95% CI: 0.22–0.94; p for interaction = 0.03). When stratified by pre- and post-pandemic period, the overall RRR was 18% (95% CI: −36–51) in pre-pandemic and 9% (95% CI: −33–37) in the post-pandemic period (Supplementary Table S3). The ratio of aRRs comparing the post- vs pre-pandemic periods was 1.15 (95% CI: 0.62–2.13; p for interaction = 0.66).

For IHD, the pooled-season RRR was 26% (95% CI: 3–43), with corresponding age-stratified estimates of 17% (95% CI: −38–50) among patients aged 65–79 years and 29% (95% CI: 4–48) among those aged ≥ 80 years (Table 2). The ratio of aRRs was 0.92 (95% CI: 0.51–1.67; p for interaction = 0.79). In the secondary analysis, the overall RRR was 3% (95% CI: −57–40) in the pre-pandemic period and 33% (95% CI: 9–51) in the post-pandemic period. The ratio of aRRs was 0.64 (95% CI: 0.36–1.12; p for interaction = 0.12) (Supplementary Table S3).

Across all one-stage pooled-season models with fewer than 10 outcomes per parameter, Firth-type penalized modified Poisson regression showed absolute RRR differences ≤1% compared to the standard modified Poisson regression models (Supplementary Table S4).

The two-stage pooled-season RRR was 6% (95% CI: −27–30%; I^2 = 17%) for ICU admission and 29% (95% CI: 7–46%; I^2 = 13%) for IHD (one-stage: 11% and 26%, respectively). Season-specific RRR estimates ranged from −60% to 62% for ICU admission, with no discernible pattern by dominant circulating influenza subtype. For

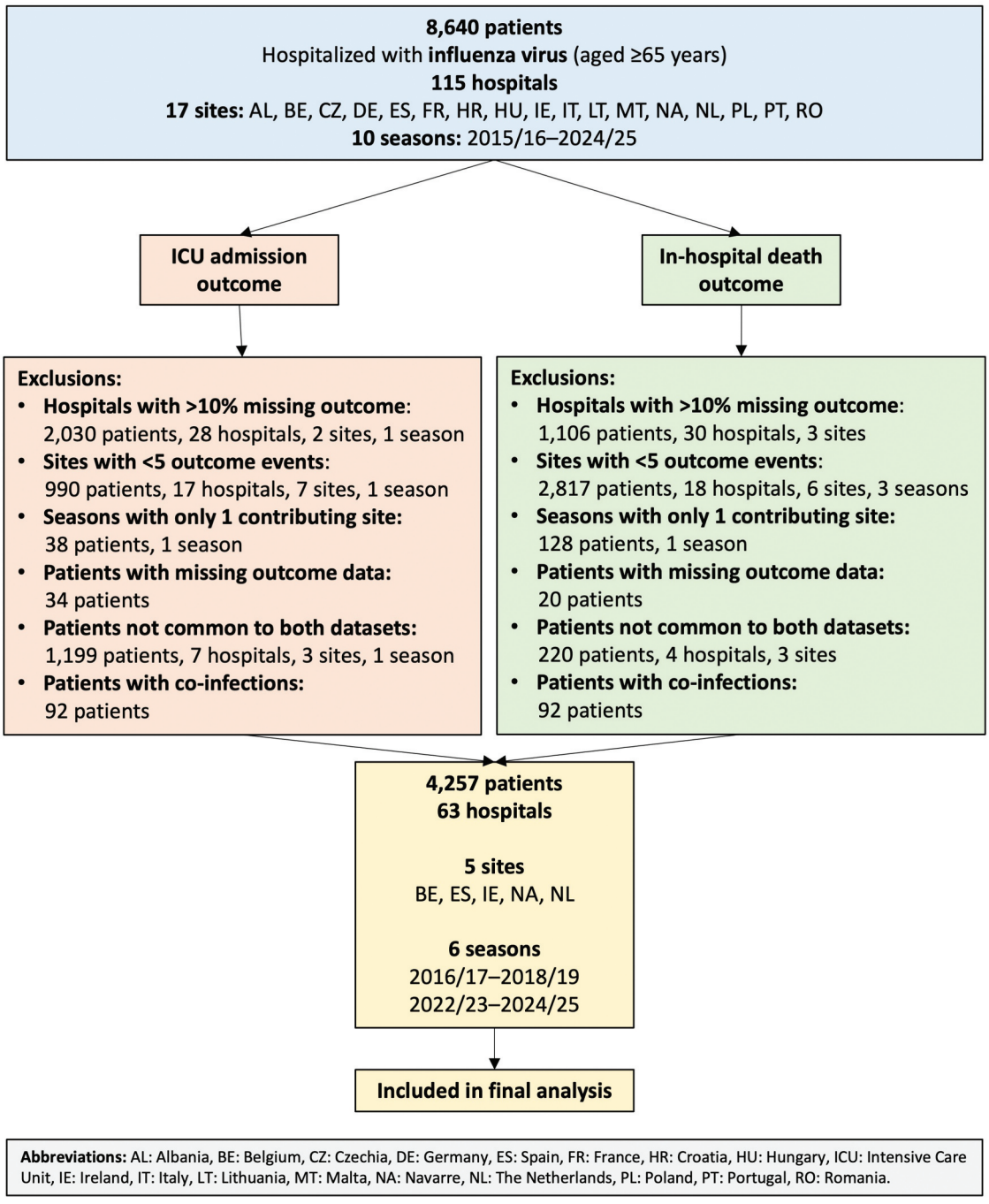

Figure 1. Flowchart of the included and excluded influenza virus-positive hospitalized patients aged ≥65 years by outcome, I-MOVE hospital network, Europe, 2015/16–2024/25.

IHD, season-specific estimates varied from −6% to 40%, with seasons having the lowest proportion of influenza A(H3N2) cases (2017/18, 2023/24, and 2024/25) yielding the highest RRR estimates (range: 36–40%), whereas seasons dominated by A(H3N2) (2016/17, 2018/19 and 2022/23) showed no observed protective association (range: −6–0%). With the exception of the A(H1N1)-dominated 2023/24 season (40%, 95% CI: 4–63%), season-specific estimates were not statistically significant (Supplementary Table S5).

Across the first three sensitivity analyses, the overall estimates for ICU admission ranged between 0% and 8% compared to 11% in main analysis; for IHD these ranged between 19% and 25% compared to 26% in main analysis (Supplementary tables S6–S8). The QBA for the overall IHD estimate gave E-values of 2.04 for the point estimate and 1.21 for the confidence interval limit closest to the null. Among adults aged ≥80 years, E-values were 2.17 and 1.25, respectively.

Table 1. Characteristics of vaccinated and unvaccinated influenza virus-positive hospitalized patients aged ≥65 years, I-MOVE hospital network, Europe, 2016/17–2024/25.

	All laboratory-confirmed influenza (≥65 years) (*N* = 4,257)			
	Vaccinated (*N* = 2,490)		Unvaccinated (*N* = 1,767)	
Characteristic	n	%	n	%
Age group (years)				
65–79	1,031	41	1,003	57
≥80	1,459	59	764	43
Sex				
Female	1,204	48	926	52
Male	1,286	52	841	48
Chronic conditions[a]				
No	318	13	344	19
Yes	2,172	87	1,423	81
Influenza vaccine type				
Standard dose[b]	1,485	72	*NA*	*NA*
Adjuvanted	358	17	*NA*	*NA*
High dose	179	9	*NA*	*NA*
Cell-propagated	54	2	*NA*	*NA*
Unknown	414	*NA*	*NA*	*NA*
Influenza virus (sub)type				
A(H1N1)pdm09	636	26	522	30
A(H3N2)	1,165	47	734	42
Influenza B	335	13	256	14
Influenza A (unsubtyped)	319	13	230	13
Influenza untyped	35	1	25	1
Season				
2016/17	369	15	207	12
2017/18	499	20	347	20
2018/19	267	11	164	9
2022/23	287	12	157	9
2023/24	407	16	341	19
2024/25	661	26	551	31

Abbreviations: NA – not applicable.
[a]Chronic conditions included at least one of: diabetes, heart disease, lung disease, asthma or immunodeficiency.
[b]Standard dose: egg-based, non-adjuvanted inactivated vaccine.

4. Discussion

Our study suggests that, among adults aged ≥65 years hospitalized with laboratory-confirmed influenza, seasonal influenza vaccination was associated with a reduction in the risk of IHD (RRR: 26%; 95% CI: 3–43), but little to no reduction in the risk of ICU admission (RRR: 11%; 95% CI: −21–34).

Our results for ICU admission were similar to those reported by Regan et al. in a multi-country analysis of four countries in South America (12%; 95% CI: −8–28) also conducted over multiple seasons (2013–2019) [21]. In contrast, studies performed in the United States during the 2013/14 season (37%; 95% CI: 19–52) [22] and Spain during the 2013/14–2014/15 seasons (65%; 95% CI: 30–83) [23] reported higher RRR estimates. This variation is consistent with the wide range observed in our season-specific results (−60% to 62%) and likely reflects that ICU admission is influenced not only by disease severity but also by patient characteristics (e.g. age), clinical guidelines, ICU bed availability, and patient or family preferences [24,25]. While these factors are unlikely to differ systematically by vaccination status, they may introduce variability when comparing estimates across different hospitals, countries and seasons. By pooling harmonized data from 63 hospitals across five study sites, our study provides a representative average of the vaccine's association across diverse countries, rather than reflecting the specific ICU admission practices of a single study site or season.

For IHD, our 26% relative reduction aligns closely with estimates from a multi-season study conducted in the United States during the 2016/17–2018/19 seasons (25%; 95% CI: 2–43), two out of three seasons with influenza A(H3N2) predominance [26]. While larger relative reductions in mortality (38–64%) have been reported [21–23,27], other studies found no statistically significant association, with estimates ranging from −15% to 44% [28–30]. These differences may reflect varying outcome definitions (e.g. 30-day mortality vs IHD) or differences in case ascertainment. A key strength of our study was the use of systematic RT-PCR testing of patients meeting the SARI case definition across most participating study sites, which minimized misclassification of influenza infection and reduced the potential for selection bias compared to studies relying exclusively on International Classification of Diseases codes or testing at clinician discretion.

Beyond differences in study population and outcome definitions, variation in estimates across studies may also reflect differences in statistical approach. While two of the studies discussed above used propensity score or inverse probability weighting methods to adjust for confounding [21,30], we used multivariable outcome regression, conditioning on the same measured covariates that would be used to construct a propensity score. Because both approaches rely on the same set of measured confounders, we would not expect this choice to be a major driver of the differences observed across studies. Consistent with this, our regression-based estimates fall within the range reported by studies using propensity score-based approaches. Variations in estimates across studies may be driven by the inclusion of different influenza seasons, characterized by variations in circulating influenza virus (sub)types and VE estimates. By spanning six seasons, our study was able to overcome the sample size limitations inherent to estimating RRR against rare outcomes such as ICU admission and IHD. Furthermore, rather than focusing on a single season with potentially atypical vaccine performance, our pooled approach provided a more representative average across varying degrees of influenza virus (sub)type predominance (Figure 2). This is contextualized by published I-MOVE hospital network VE estimates, where VE against laboratory-confirmed hospitalized influenza among patients aged ≥ 65 years ranged between 13% and 47% across included seasons (Supplementary Table S9).

Stratification by age group yielded comparable estimates for IHD among adults aged 65–79 years and ≥80 years (RRR: 17% vs 29%, respectively). In contrast, evidence of effect modification by age was observed for ICU admission ($p = 0.03$), with a greater estimated risk reduction among those aged ≥ 80 years (RRR: 44%, 95% CI: −11–72) compared to little or no reduction among those aged 65–79 years (RRR: −4%, 95% CI: −46–25). However, interpretation of age-specific associations for ICU admission warrants caution because, consistent with the literature [4], ICU admission in our cohort was less frequent in adults aged ≥80 years compared to those aged 65–79 years (occurring in 1% vs 6% of vaccinated, and 3% vs 7% of unvaccinated, respectively). This low frequency is strongly influenced by ICU-triage protocols and care-limitation decisions (e.g. advance directives or do-not-resuscitate orders) [24,25]. This may result in lower precision and may create a selection bias, where the adults

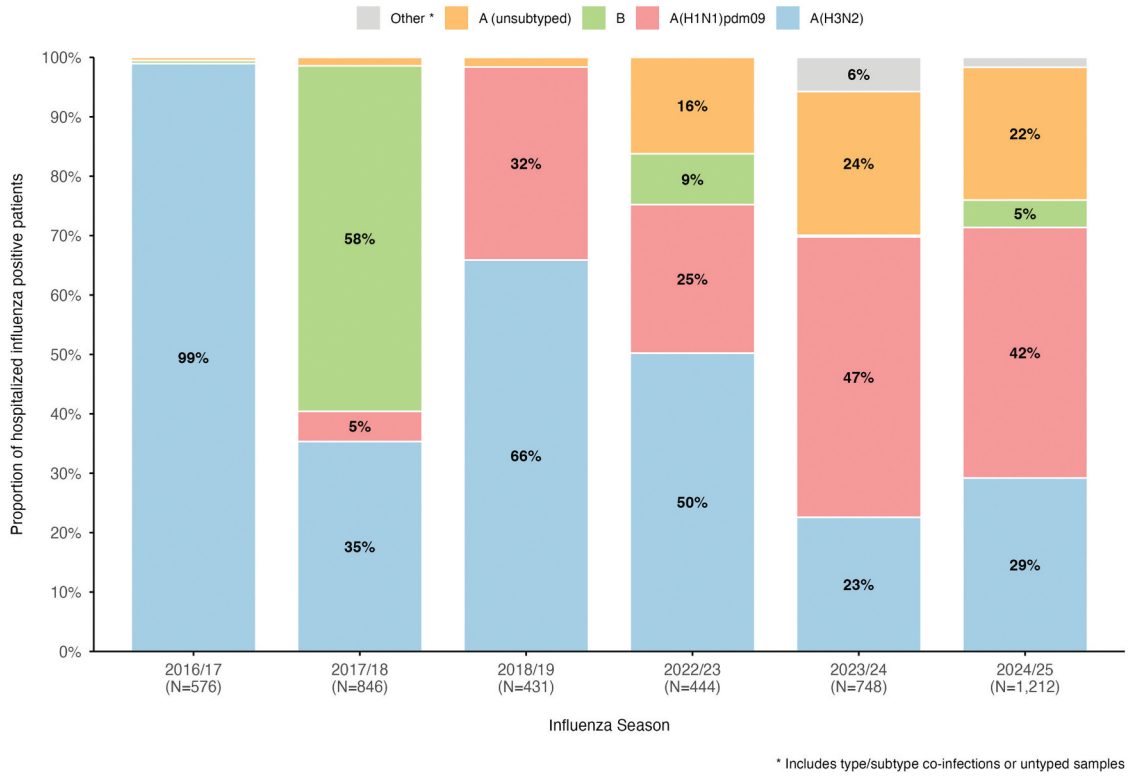

Figure 2. Distribution of (sub)types among influenza virus-positive hospitalized patients aged ≥65 years, by season, I-MOVE hospital network, Europe, 2016/17–2024/25.

Table 2. Confounder-adjusted relative risk reduction for ICU admission and in-hospital death among influenza virus-positive hospitalized patients aged ≥65 years, by outcome and age group, I-MOVE hospital network, Europe, 2016/17–2024/25.

Outcome and age group	Risk of outcome among vaccinated: % (n/N)	Risk of outcome among unvaccinated: % (n/N)	Crude RR	95% CI	Confounder-adjusted RR[a]	95% CI	Relative risk reduction (%)	95% CI
ICU admission								
Overall	3% (81/2,490)	5% (89/1,767)	0.65	0.48–0.87	0.89	0.66–1.21	11	−21–34
65–79 years	6% (65/1,031)	7% (69/1,003)	0.92	0.66–1.27	1.04	0.75–1.46	−4[+]	−46–25
≥80 years	1% (16/1,459)	3% (20/764)	0.42	0.22–0.8	0.56	0.28–1.11	44[+#]	−11–72
In-hospital death								
Overall	5% (119/2,490)	5% (96/1,767)	0.88	0.68–1.14	0.74	0.57–0.97	26	3–43
65–79 years	3% (26/1,031)	3% (31/1,003)	0.82	0.49–1.36	0.83	0.50–1.38	17[+]	−38–50
≥80 years	6% (93/1,459)	9% (65/764)	0.75	0.55–1.02	0.71	0.52–0.96	29[+]	4–48

Abbreviations: RR, risk ratio; CI, confidence interval; n, number of patients with the outcome; N, total number of patients.
[a]Adjusted for age, sex, presence of ≥1 chronic condition, admission date, season and study site. The selected models parameterized time as an additive fixed effect for season and a restricted cubic spline (RCS) of the admission date (modeled as a continuous daily index with 3 knots); age was modeled as a linear term or an RCS with 3–4 knots.
[+]Total number of outcomes divided by 10 smaller than the number of model parameters; Firth-type penalized modified Poisson regression showed no evidence of small-sample bias (difference <10% points).
[#]Total number of outcomes divided by 10 smaller than the number of contributing study sites.

aged ≥ 80 years admitted to ICU represent a specific subgroup of 'healthier' older patients deemed capable of withstanding intensive treatment. Consequently, this group may not be representative of the broader population aged ≥80 years, who often present with higher levels of frailty. Furthermore, because the observed 44% RRR is based on a low number of events and has a wide 95% CI (−11–72), this estimate could also be explained by random error.

Our secondary analysis showed no statistically significant differences between pre- and post-pandemic periods for either outcome (p for interaction ≥0.12). This is further supported by the low between-season heterogeneity (I^2 ≤17%) and the consistency between one-stage and two-stage pooled estimates (Supplementary Table S5). While the formal test for interaction was non-significant, we observed a lower RRR for IHD in the pre-pandemic period (3%) than the post-pandemic

period (33%). As patient characteristics remained stable across these periods (Supplementary Table S2), the variation in RRR may be explained by differences in subtype circulation or increased usage of enhanced vaccine formulations, such as high-dose or adjuvanted vaccines. The pre-pandemic seasons included were characterized by a higher relative proportion of influenza A(H3N2) (62%) compared to post-pandemic seasons (31%). This is consistent with subtype-specific RRR estimates provided by Regan et al. who reported a lower RRR among influenza A(H3N2) cases than among influenza A(H1N1)pdm09 or influenza B cases [21]. This relationship is also reflected in our season-specific RRR results, which showed a lack of protective association against IHD during A(H3N2) predominant seasons. While the shift toward enhanced vaccines in the post-pandemic period may have contributed to higher RRR, our study was not sufficiently powered to evaluate RRR by vaccine type. However, recent evidence suggests that these formulations may provide greater protection against influenza-associated hospitalization [31] and higher reductions in influenza-associated mortality following hospitalization [26] compared to standard-dose vaccines.

Our study has some limitations. Firstly, unmeasured confounding related to underlying vulnerability remains possible. Although we adjusted for the presence of key chronic conditions, detailed frailty measures, socioeconomic variables (e.g. health literacy), or healthcare utilization indicators (e.g. the number of previous hospitalizations or outpatient visits) were unavailable, precluding further confounding adjustment. While a 'healthy vaccinee' bias cannot be ruled out (which would overestimate the protective association), we anticipate that confounding by indication (frailty bias) is more likely. As the most vulnerable older adults are preferentially targeted for vaccination, vaccinated individuals in our hospitalized cohort likely possess a higher baseline risk for severe outcomes than their unvaccinated counterparts. Consequently, we expect this unmeasured confounding to pull our estimates toward the null, potentially underestimating the strength of the observed protective associations. Adjustment for antiviral therapy in hospital was likewise not possible, as information on antiviral use and timing during hospitalization was not available. Because early antiviral treatment reduces the risk of severe outcomes [32,33], differential use by vaccination status or delays in administration could have attenuated or inflated the observed associations. The E-values observed in our QBA sensitivity analysis suggested that an unmeasured confounder would need to be associated with both vaccination and mortality by a risk ratio of at least 2.04 to fully explain our finding, or by a risk ratio of 1.21 to shift our confidence interval to include the null. Such a confounder would need to operate in the direction of a healthy-vaccinee effect (i.e. associated with both a higher likelihood of vaccination and a lower risk of IHD), which is less likely than confounding by indication (frailty bias) in our study population. We therefore consider it unlikely that unmeasured confounding fully explains our findings. However, as with any observational study, we cannot fully exclude this possibility.

Secondly, although a common protocol and standardized outcome definitions were applied across all study sites, we cannot fully exclude the possibility that ICU admission was not captured with the same completeness everywhere. Differences in health system organization (e.g. availability of high-dependency units) or in capacity during periods of strain (e.g. during the COVID-19 pandemic) could mean that some ICU-level care was delivered outside formally designated ICU wards and therefore may not have been captured under our ICU admission indicator. We would not expect this to differ by vaccination status within a given site or season; however, if the completeness of ICU capture varied across sites or seasons, this could contribute to the variability observed in our season-specific estimates, independent of any difference in the vaccine–outcome association. Due to sample size constraints, we did not estimate site-specific associations or test for site-level heterogeneity.

Thirdly, our study only considered in-hospital deaths, as 30-day post-admission mortality data were not available across all study sites. This restriction introduces a potential discharge bias, as patients may have been discharged to palliative care facilities or died shortly after discharge, leading to an under-ascertainment of fatal outcomes. Additionally, if individuals who die in hospital are more likely to be unvaccinated than those who died after discharge [34], using in-hospital mortality as an endpoint could lead to a differential under-ascertainment of deaths among vaccinated patients, potentially overestimating the observed RRR.

Fourthly, the exclusion of hospitals with >10% missing outcome data or the use of an aligned cohort for both outcomes reduced sample size and limited representativeness. However, these approaches were implemented to minimize reporting bias and ensure comparability between outcomes. Additionally, sensitivity analyses showed that the inclusion of these records did not alter the interpretation of our findings.

Fifthly, while our pooled sample size was sufficient for the primary analysis, it was insufficient for further stratification by influenza (sub)type and season. Given the low RRR observed, larger cohorts are required to provide the statistical power necessary for precise estimates within subgroups. Furthermore, incomplete information and sample size limitations precluded the exploration of the effects of use of different vaccine types (e.g. adjuvanted or high-dose vs standard-dose vaccines) [26], prior-season vaccination [23], or estimation of the RRR in younger age groups.

Sixthly, RSV testing in older adults was not systematically implemented in the pre-pandemic period, and in the post-pandemic period some study sites may have utilized sequential testing algorithms (e.g. performing SARS-CoV-2 testing only if influenza virus RT-PCR was negative or vice-versa). As a result, some co-infections may have been undetected. In our sensitivity analysis including the 92 identified co-infection cases, the RRR estimates were slightly lower but varied by less than five percentage points (Supplementary Table S8). This suggests that if undetected co-infections remained in the main analysis, our results might represent a slight underestimation of the RRR. However, based on the low frequency of identified co-infections in our cohort, it is unlikely that undetected co-infections significantly influenced the observed associations.

Finally, restricting the analyses to patients hospitalized with laboratory-confirmed influenza limits comparability between vaccinated and unvaccinated individuals, as vaccination may have prevented hospitalization among less vulnerable individuals, and vaccinated patients who are hospitalized may differ from unvaccinated patients in underlying vulnerability [35–37]. Consequently, the associations obtained in this study should not be interpreted as estimates of vaccine effectiveness against progression to ICU admission or IHD, but rather as associations between vaccination status and the relative risk of in-hospital severe outcomes.

5. Conclusions

Our study found that the estimated risk reduction against ICU admission was 11%, with confidence intervals compatible with little or no reduction in risk. In contrast, influenza vaccination was associated with a 26% relative reduction in the risk of death in hospital among adults aged ≥ 65 years hospitalized with laboratory-confirmed influenza, corresponding to approximately a one-quarter reduction in the risk of death compared to unvaccinated individuals. This finding suggests that vaccination is associated with reduced disease severity even when hospitalization was not prevented. This reinforces the potential added value of influenza vaccination in reducing fatal in-hospital outcomes among older adults and supports continued efforts to improve vaccine uptake in this high-risk population.

Continued harmonized multicenter hospital studies are needed to assess the consistency of these associations across future influenza seasons and to increase precision for these outcomes. Because ICU admission may reflect more than just disease severity, future studies could explore alternative severity endpoints, such as the requirement for mechanical ventilation or the use of standardized organ failure scores, that better capture influenza-related severity among hospitalized older adults.

Declaration of interests

Ligita Jančorienė has received honoraria fees for lectures from Swixx and AbbVie. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The corresponding author declares the use of Google Gemini (Gemini 1.5 Pro) for coding assistance and language improvement after preparation of the initial draft. After using this tool, the text was updated after review by coauthors with no further use of AI. All authors take full responsibility for the content of the manuscript, and confirm that all generative AI use complies with Taylor & Francis' policy on the responsible use of generative AI.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Ethics statement

The planning, conducting and reporting of the studies were in line with the Declaration of Helsinki. Official ethical approval was not required if studies were classified as being part of routine care/surveillance (Ireland, Italy, Malta, Scotland and Spain/National for the VEBIS-project seasons). Verbal informed consent was required from patients for participation in any further research (including VE studies). Other study sites received local ethical approval from a national or regional review board.

Belgium: the study protocol was approved by the central Ethical Committee (CHU Saint- Pierre [AK/12-02-11/4111] initially in 2011 and UZ VUB [B.U.N. 143201215671] from 2014 on) and each participating hospital's local ethical committees in 2011 (AK/12-02-11/4111), and updated from 2014 (UZ-Brussel en VUB B.U.N. 143201215671). The most recent amendment was approved on 27 September 2023 (reference 2012/310 Am6).

Germany: SARI surveillance was approved by the Charité-Universitätsmedizin Berlin Ethical Board (Reference EA2/126/11 and EA2/218/19).

Croatia: approved by the Ethics committee of the Croatian Institute of Public Health on 25 September 2015 (3-year approval), 21 November 2018, 7 November 2019, 26 November 2020, 24 May 2021, 26 January 2022, 20 June 2022, 3 July 2023 and 29 November 2024, Number: 80-2661/1-15; Class: 030-02/18-01/1, Number: 381-10-18-2; Class: 030-02/18-01/1, Number: 381-15-19-4; Klasa: 030-02/20-01/3, Number 381-15-20-2; Class: 030-02/21-01/1, Number: 381-15-21-7; Class: 030-02/21-01/1, Number: 381-15-22-14, Class: 030-02/22-01/2, Number: 381-15-22-2, Class: 030-02/23-01/3, Number: 117-15-23-3; Class: 030-02/24-01/1, Number: 117-15-24-2; Class: 030-02/24-01/1.

France: the data are draw from the Respivac Study, approved by the French Ethical Committee CPP EST III (clinicaltrial.gov number: NCT05582239, ID-RCB: 2022-A01056-37).

Hungary: approved by the National Scientific and Ethical Committee (ETT/TUKEB 56025-3/2014/EKU; ETT/TUKEB 44088–3/2015/EKU; IV/1885-5/2021/EKU);.

Lithuania: approved by Kaunas Regional Biomedical Research Ethics Committee for influenza seasons 2015–2020 (Nos P1-158200-04-476-138/2012, P2-158200-04-476-138/2012, P3-158200-04-476-138/2012, P4-158200-04-476-138/2012, P5-158200-04-476-138/2012, P6-158200-04-476-138/2012, P7-158200-04-476-138/2012), and approved by Lithuanian Bioethics Committee on 3 July 2020, and later permission extended for the study period for seasons 2020–2025, No. L-20-3/1-2.

Spain/Navarre: approved by the Navarre Ethical Committee for Medical Research (Pyto2015/95, EO2021/21 and PI_2023/145).

The Netherlands: the Dutch Medical Research Involving Human Subjects Act (Dutch acronym: WMO) did not apply, because only fully anonymous data were used and there were no interventions other than routine clinical care. A waiver for full medical ethical review was obtained from the Medical Ethical Committee of the University Medical Center Utrecht, reference No. WAG/om/15/034147.

Poland: approved by the Ethics Committee in the NIPH NIH, document name: Opinia nr 3/2010 z dnia 23.09. 2010r. i aneks z dnia 16 December 2014r. do opinii nr 3/2010.

Portugal: approvals and/or amendments 22 May 2015, 28 September 2026, 12 December 2018, 28 April 2020, 19 January 2021, 7 June 2022 by the Ethics Committee of Instituto Nacional de Saúde Dr Ricardo Jorge, no registration number given;.

Romania: approved by the Ethics Committee of the Ministerul Apărării Naionale Institutul Naional de Cercetare pentru Dezvoltare Medico-Militară 'Cantacuzino' (46/2015, 106/2016, 251/2017, 313/2018, 299/2019, 12/2020, 236/2022, 344/2023, 388/2024); approved by the INSP Romania Scientific Council – Ethics Committee (24530/2022, 23468/23, 19139/2024, 18218/2025).

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Aragón: PI19/430 1 April 2020, Andalucía: code f12f8377d78c34a25-d6935eff535cd26715e2b8c, 15 April 2020).

Data availability statement

Restrictions apply to the availability of these data, which were used under specific institutional data-sharing agreements for the current study. The data that support the findings of this study are available from the corresponding author upon reasonable request and with the explicit permission of the participating study site institutions and the study funder (ECDC).

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Author contributions

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ORCID

Diogo F. P. Marques http://orcid.org/0000-0002-2556-0923
Angela M. C. Rose http://orcid.org/0000-0002-2493-8082
Susana Monge http://orcid.org/0000-0003-1412-3012
Iván Martínez-Baz http://orcid.org/0000-0002-3405-2277
Marijke Reynders http://orcid.org/0000-0003-2079-1279
Róisín Duffy http://orcid.org/0009-0001-7169-9109
Sierk D. Marbus http://orcid.org/0000-0002-7457-6964
Liem Binh Luong Nguyen http://orcid.org/0000-0002-5235-0868
Goranka Petrović http://orcid.org/0000-0001-8304-5519
Beatrix Oroszi http://orcid.org/0000-0001-8915-0336
Antonino Bella http://orcid.org/0000-0002-6615-4227
Monika Kuliese http://orcid.org/0000-0002-4601-4585
Stephen Abela http://orcid.org/0009-0005-0314-1022
Iwona Paradowska-Stankiewicz http://orcid.org/0000-0001-7222-1337
Ausenda Machado http://orcid.org/0000-0002-1849-1499
Odette Popovici http://orcid.org/0000-0003-4157-2622
Francisco Pozo http://orcid.org/0000-0003-1828-733X
Ana S. Lameiras Azevedo http://orcid.org/0000-0001-6692-5944
Camino Trobajo-Sanmartín http://orcid.org/0000-0001-5105-252X
Anna Parys http://orcid.org/0000-0001-8265-7070
Lisa Domegan http://orcid.org/0000-0002-7483-6703
Arianne B. van Gageldonk-Lafeber http://orcid.org/0000-0002-0342-2087
Kristin Tolksdorf http://orcid.org/0000-0002-8712-6399
Vesna Višekruna Vučina http://orcid.org/0009-0009-8954-6846
Gergő Túri http://orcid.org/0000-0003-3465-8321
Flavia Riccardo http://orcid.org/0000-0002-1582-6329
Ligita Jančorienė http://orcid.org/0000-0001-6488-6312
John Paul Cauchi http://orcid.org/0000-0001-8983-8499
Verónica Gómez http://orcid.org/0000-0003-0485-0005
Mihaela Lazar http://orcid.org/0000-0002-8226-6026
Baltazar Nunes http://orcid.org/0000-0001-6230-7209

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